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Long-Term Exposure to Traffic-Related Air Pollution and Risk of Incident Atrial Fibrillation: A Cohort Study

Maria Monrad[1], Ahmad Sajadieh[2], Jeppe Schultz Christensen[1], Matthias Ketzel[3], Ole Raaschou-Nielsen[1,3], Anne Tjønneland[1], Kim Overvad[4], Steffen Loft[5], and Mette Sørensen[1]

[1] *Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark*

[2] *Department of Cardiology, Copenhagen University Hospital of Bispebjerg, Bispebjerg Denmark*

[3] *Department of Environmental Science, Aarhus University, Roskilde, Denmark*

[4] *Section of Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark*

[5] *Section of Environmental Health, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

Correspondence: Maria Monrad, Diet, Genes and Environment, Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen Ø, Denmark. E-mail: marim@cancer.dk, Tel.: 004535257714

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Short title: Air pollution and atrial fibrillation

Abstract

Background: Atrial fibrillation is the most common sustained arrhythmia and associated with cardiovascular morbidity and mortality. The few studies conducted on short-term effects of air pollution on episodes of atrial fibrillation indicates a positive association, though not consistently.

Objectives: The aim of this study was to evaluate the long-term impact of traffic-related air pollution on incidence of atrial fibrillation in the general population.

Methods: In the Danish Diet, Cancer, and Health cohort of 57,053 people aged 50-64 years at enrolment in 1993-1997, we identified 2,700 cases of first-ever hospital admission for atrial fibrillation from enrolment to end of follow-up in 2011. For all cohort members, exposure to traffic-related air pollution assessed as nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) was estimated at all present and historical residential addresses from 1984 to 2011 using a validated dispersion model. We used Cox proportional hazard model to estimate associations between long-term residential exposure to NO_2 and NO_x and risk of atrial fibrillation, after adjustment for lifestyle and socioeconomic position.

Results: A 10 $\mu g/m^3$ higher 10-years' time-weighted mean exposure to NO_2 preceding diagnosis was associated with an 8 % higher risk of atrial fibrillation (incidence rate ratio: 1.08; 95% confidence interval: 1.01-1.14) in adjusted analysis. Though weaker, similar results were obtained for long-term residential exposure to NO_x. We found no clear tendencies regarding effect modification of the association between NO_2 and atrial fibrillation by sex, smoking, hypertension or myocardial infarction

Conclusion: We found long-term residential traffic-related air pollution to be associated with higher risk of atrial fibrillation. Accordingly, the present findings lend further support to the demand for abatement of air pollution.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with increased risk for ischemic and embolic stroke and myocardial infarction (Schnabel et al. 2015). Patients with symptomatic AF tend to experience reduced cardiac performance, exercise capacity and quality of life (Go et al. 2001; Miyasaka et al. 2006). AF affects approximately 4 % of the population age 50 years and over, but the aetiology is complex and not fully understood (Go et al. 2001).

Exposure to short- and long-term ambient air pollution has been associated with cardiovascular morbidity and mortality, including myocardial infarction and stroke (Brook et al. 2010; Watkins et al. 2013). Only few short-term studies have examined associations between ambient air pollution and having an episode of AF with inconsistent results. No published study appears to have focused specifically on AF in relation to long-term exposure to air pollution. A few studies have investigated the association with mortality from cardiac rhythm disturbances: one study found that residential $PM_{2.5}$ assessed by ambient air monitors was associated with a higher risk (Pope et al. 2004), whereas two other studies failed to show any associations with exposure to $PM_{2.5}$ and NO_2 assessed by modelling (Beelen et al. 2009; Raaschou-Nielsen et al. 2012). Furthermore, one study has examined association between long-term air pollution and incident cardiac rhythm disturbances and found no associations with PM_{10}, NO_2 or SO_2 assessed by emission-based models (Atkinson et al. 2013).

Exposure to air pollution might lead to AF through different mechanisms. Deposition of PM in the lung, with or without translocation into the bloodstream, has in controlled human exposure studies been found to induce local and systemic inflammation (Behbod et al. 2013; Graff et al. 2009; Kajbafzadeh et al. 2015). Systemic inflammation has in various studies been associated with an increased risk of AF (Dewland et al. 2015; Issac et al. 2007). Moreover, exposure to PM has been found to directly affect sensory receptors in the lung leading to alterations in the autonomic nervous system (Perez et al. 2015), which may induce changes of atrial electrophysiology and thereby play an important role in the initiation of AF (Chen et al. 2014; Shen and Zipes 2014). Dysfunction of the autonomic nervous system can enhance inflammation further, and consequently this could work like a vicious circle (Tracey 2002). Besides these mechanisms, exposure to PM is known to cause oxidative stress which is suspected of inducing AF, e.g. through increasing inflammation and by damaging myofibrils, thereby potentially remodelling atrial structure (Miller et al. 2012; Youn et al. 2013). The small size of traffic-related PM, especially ultrafine particles from diesel engine emission, have a high alveolar deposition, large surface area and adhered toxic compounds including reactive oxygen species, and may therefore be particularly harmful in these mechanisms (Miller et al. 2012).

The aim of the present study was to investigate the association between residential exposure to long-term traffic-related air pollution, using NO_2 and NO_x as indicators of air pollution from traffic including particulate matter, and risk of incident AF in a large cohort.

Methods

Study population

The present study was based on the Danish Diet, Cancer, and Health study (Tjonneland et al. 2007). Between 1993 and 1997 individuals, aged 50-64 and living in Copenhagen or Aarhus were invited to participate, adding up to 160,725 individuals, from which 57,053 (35 %) persons agreed to participate in the cohort. The participants had to be born in Denmark with no history of cancer at the time of enrolment. At enrolment, each participant completed self-administered, interviewer-checked, lifestyle questionnaires covering smoking habits, diet, alcohol consumption, physical activity and education. The participants reported their current and past smoking habits of cigarettes, cheroots, cigars and pipes. The quantity of tobacco smoked each day (smoking intensity) was calculated by converting the amount of each kind of tobacco into grams of tobacco by equating a cigarette to 1 gram, a cheroot or a pipe to 3 gram and a cigar to 5 gram of tobacco. Also, height, weight, waist circumference and systolic and diastolic blood pressure were measured by trained staff members according to standardized protocols. The study was conducted in accordance with the Helsinki Declaration and approved by the local Ethics Committees and written informed consent was obtained from all participants.

Outcome definition

Cases with AF diagnosed between baseline and death, emigration, or end of follow-up (31 December 2011) were identified by linking the unique personal identification number of each cohort member to the nationwide Danish National Patient Register (Lynge et al. 2011). Since 1977 patients with any disease diagnosed in-hospital have been registered in the Danish National Patient Register and since 1995 diagnoses from emergency rooms and outpatient visits have been registered as well (Lynge et al. 2011). Cases were identified using discharge diagnosis according to the International Classification of Diseases (ICD) 8 codes 427.93 and 427.94 and ICD 10 code I48.9. We considered only the first hospitalization of AF. In Denmark all patients discharged from a hospital, an emergency room or an outpatient clinic are registered into the National Patient Registry using the ICD10 (ICD8 before 1995). According to Danish and European guidelines all patients with AF are ultimately referred to the hospital system for echocardiography and cardiology evaluation.

Exposure Assessment

Residential address history for all cohort members between 1st of January 1984 and event or end of follow-up at 31th December 2011 was collected from the Danish Civil Registration

System (Pedersen 2011). Concentrations of ambient NO_2 and NO_x were calculated with the Danish AirGIS modelling system (dispersion model), for each year (1984-2011) at each address at which the cohort members had lived. NO_2 and NO_x were used as indicators for air pollution, as they are considered good markers of traffic-related air pollution, and NO_x correlates closely with PM in Danish streets: $r = 0.93$ for total particle number concentration [size 10–700 nm (ultrafine particles)] and $r = 0.70$ for PM_{10} (Hertel et al. 2001; Ketzel et al. 2003). The Danish AirGIS modelling system calculates air pollution as the sum of regional background, urban background, and local street level calculated with the Operational Street Pollution Model (OSPM) (Berkowicz et al. 2008; Jensen et al. 2001; Kakosimos et al. 2010). Urban background concentration is calculated in a 1km x 1km resolution taking into account emissions from all sectors provided in the same spatial resolution, while the local street contribution is calculated at the building façade near the closest and most trafficked road with a few meters resolution. Input data for the AirGIS system included geographical coordinates for each address; road links with information on annual average daily traffic (average daily traffic on a roadway link during a period of one year expressed in vehicles per day), vehicle distribution (of light and heavy vehicles), travel speed, road type, emission factors for the Danish car fleet all including historic trends, street and building geometry, building height and meteorological data. We obtained traffic counts for all Danish roads with more than 1000 vehicles per day from a national road and traffic database, that includes an estimate about the historic changes in traffic back to 1960 (Jensen et al. 2009). The AirGIS system has been successfully validated in various studies (Berkowicz et al. 2008; Jensen; et al. 2009; Ketzel et al. 2011). A validation study comparing modelled and measured NO_2 has been conducted. The NO_2 concentrations were measured in the years 1994-1995 using samplers placed at 204 positions in the greater Copenhagen area. At each location NO_2 concentrations were measured during a consecutive period of 6 months with a sampling period of 1 month. The comparison between modelled and measured half-year mean NO_2 concentrations showed a correlation coefficient (R^2) of 0.81, being on average 11% lower than those modelled (Berkowicz et al. 2008). Also, modelled and measured 1-month mean concentrations of NO_x and NO_2 over 12 years (1995–2006) on a busy street in Copenhagen (Jagtvej, 25,000 vehicles per day, street canyon) was correlated with correlation coefficients of 0.88 for NO_x and 0.67 for NO_2. The modelled mean concentration over the whole 12-year period was 6% lower than the measured concentrations of NO_x and 12% lower than those of NO_2 (Ketzel et al. 2011). Thus, the model predicted both geographical and temporal variation well.

Statistical analyses

The analyses were based on a Cox proportional hazards model with age as underlying time-scale (Thiebaut and Benichou 2004). Left truncation at age of enrolment was used so that people were considered at risk from the exact age they had at the day they were enrolled into the cohort (delayed entry). All participants with a diagnosis of AF before enrolment were excluded. Right censoring was used at the age of AF (event), death, emigration or end of follow-up (31th December 2011), which ever came first. Exposure to NO_2 and NO_x were modelled, as time-weighted mean air pollution during the 1-, 5- and 10-years' preceding diagnosis taking all present and historical addresses in these periods into account. The exposure windows (1-, 5- and 10-years) were entered as time-dependent variables into the statistical risk model, thus for each case of AF recalculating exposure for all cohort participants (at risk) at exactly the same age as the case at the time of diagnosis. To control for trends over time in outcome/exposure we adjusted for calendar-year which was estimated as an underlying time-dependent variable in 5-years intervals (1992-1997, 1997-2002, 2002-2007, and 2007-2012).

Incidence rate ratios (IRR) for the association between the two air pollution estimates and AF were analysed crudely and adjusted for potential baseline confounders defined *a priori*: sex, body mass index (BMI; kilograms per meter squared), waist circumference (centimetres), smoking status (never, former, current), smoking duration (years), smoking intensity (lifetime average, gram tobacco/day), alcohol consumption (yes, no), intake of alcohol (gram/day), physical activity (yes, no), sport during leisure time (hours/week), length of school attendance (≤ 7, 8-10, > 10 years) and area level socioeconomic position of the participant's enrolment municipality (or district for Copenhagen; 10 districts in total) classified as low, medium or high, based on municipality/district-level, information on education, work market affiliation and income, occupational status (employed, unemployed/ retired) and calendar-year. In an additional analysis, we included area level socioeconomic position as random effect in the Cox model.

We also performed analyses with five categories of exposure to 10-years' time-weighted exposures of NO_2 and NO_x according to quintiles among cases and estimated IRR of AF using the lowest quintile as reference.

The assumption of linearity of NO_2, NO_x and continuous covariates were evaluated visually and by formal testing (Wald's test) with linear spline models with nine knots placed at deciles for cases. We found NO_x to deviate from linearity ($p = 0.03$), and therefore associations between NO_x and AF were analysed using categories of NO_x (quintiles). NO_2 did not deviate from linearity ($p = 0.10$), and associations between NO_2 and AF were therefore analysed both categorical (quintiles) and linearly (per 10 $\mu g/m^3$). We also found smoking intensity to deviate from linearity, and included this covariate as a spline with cut-point at 20 g/day. This cut-point was determined by visual examination of the linear spline model, followed by a formal testing of whether we could assume linearity of the variable below and above the cut-point. The remaining covariates did not deviate from linearity.

We estimated whether there was an effect modification of the association between NO_2 and AF according to: sex (men/women), smoking status (ever/never), area level socioeconomic position (low/medium/high), baseline hypertension (yes/no), diagnose of myocardial infarction (before censoring; yes/no) and a diagnose of diabetes (before censoring though only until 2006; yes/no). Potential modification was evaluated by introducing an interaction term into the model and tested by Wald test. Baseline hypertension was defined as having systolic blood pressure greater than 140 mm Hg or diastolic pressure greater than 90 mm Hg, measured by an automatic blood pressure device (Takeda Medical UA 751 or UA-743) at enrolment and/or answering yes to the following question in the baseline questionnaire: "Do you suffer, or have you ever suffered from high blood pressure?". Information on diagnosis of myocardial infarction before censoring was obtained by linkage of all cohort members unique personal identification number with the Danish National Patient Registry using ICD-8 (410) and ICD-10 (DI21). We also analysed whether the association between NO_2 and AF diagnosed before the age of 67.5 years was different from the association between NO_2 and AF diagnosed after the age of 67.5 years. Diabetes cases were identified by linkage with the Danish National Diabetes Registry (Carstensen et al. 2008), for which we had information until 2006. All analyses were performed using SAS version 9.3 (SAS Institute, North Carolina, USA).

Results

Out of the 57,053 enrolled cohort participants, we excluded 572 participants with a diagnosis of cancer before enrolment, 1,015 participants with a diagnosis of AF before enrolment, 2,719 participants with incomplete residential address history in the period from 1st of January 1984 to censoring and 2,276 participants with missing data on one or more covariates, leaving a study population of 50,399 participants. Among these, 2,700 participants were diagnosed with incident AF, during a mean follow-up time of 14.7 years.

The baseline median exposure to NO_2 for the whole cohort was 16.6 μg/m^3, ranging from the lowest value of 8.5 μg/m^3 to a maximum of 65.3 μg/m^3. For NO_x the baseline median exposure was 20.8 μg/m^3 ranging from 10.3 μg/m^3 to 379.6 μg/m^3. The Spearman correlation between 10-years' exposure to NO_2 and NO_x was 0.97. The three exposure windows, 1-, 5- and 10-years' time-weighted mean, were highly correlated, with Spearman's correlation coefficients of above 0.90 for NO_2 and 0.89 for NO_x.

Distribution of baseline covariates among cohort participants according to low, medium and high NO_2 exposure can be seen in Table 1. We observed that subjects living at residences with medium and high exposure to NO_2 tended to have a higher socioeconomic position, more often be heavy smokers and drinkers and have a higher occurrence of hypertension and history of myocardial infarction as compared with participants with low NO_2 exposure. Less subjects living with high NO_2 tended to be physically active as compared with participants with low and medium NO_2 exposure (Table 1).

A 10 μg/m^3 higher 10-years' time-weighted mean exposure to NO_2 was associated with an 8 % (IRR = 1.08; 95% CI=1.01-1.14) higher risk of AF after adjustment (Table 2). The association between NO_2 and AF seemed to follow a linear exposure-response relationship until around 18 μg/m^3 with a possible levelling off at higher exposure levels, although the confidence intervals for each category were widely overlapping (Supplement Figure S4). Including area level socioeconomic position as a random effect resulted in only minor changes in the estimates (1.08; 95% CI: 1.02-1.14). Exposure to NO_2 for the two shorter exposure windows showed that a 10 μg/m^3 increase in 1-year and 5-years' time-weighted mean exposure preceding diagnosis was associated with a 7 % (IRR=1.07; 95% CI=1.00-1.13) and an 8 % (IRR=1.08; 95% CI=1.02-1.15) higher risk of AF, respectively (Supplemental Table

S1, supplement Figure S2). Exposure to more than 16.9 μg/m^3 10-years' time-weighted mean NO_x was associated with an increased risk of AF (Table 2). As found in the test for linearity, the association between exposure to NO_x and risk of AF deviated from linearity (Supplement Figure S1 and S3).

In Figure 1 associations between 10-years' time-weighted exposures of NO_2 and risk of AF in different subgroups are shown. There were no statistically significant differences of the association between exposure to NO_2 and AF by sex, area level socioeconomic position, smoking status, hypertension, myocardial infarction or diabetes, and no differences in estimates according to age at AF diagnosis. However, there was an indication of a stronger association between NO_2 and AF among participants with a diagnosis of hypertension (IRR=1.11; 95% CI= 1.04-1.20) as compared with no diagnosis of hypertension (IRR=1.02; 95% CI= 0.92-1.12).

Discussion

We found a positive association between long-term residential exposure to traffic-related air pollution and risk of AF, which for NO_2 seemed to follow a linear exposure-response relationship with level off after 18 μg/m^3. There were no clear tendencies regarding effect modification by sex, smoking status, hypertension or myocardial infarction in the association between air pollution and AF, and no differences in estimates according to age at AF diagnosis.

The present study is the first to specifically study associations between long-term air pollution and AF. Because of the absence of historical address data, most studies used short-term air-pollution assessed at the residential address at the time of AF**.** Five previous studies have investigated the association between short-term exposure to air pollution and episodes of AF (Bunch et al. 2011; Liao et al. 2011; Link et al. 2013; Milojevic et al. 2014; Rich et al.

2006). Although the studies are not consistent, most of them indicate that exposure to air pollution, over hours and days, is associated with increased risk of AF (Liao et al. 2011; Link et al. 2013; Milojevic et al. 2014; Rich et al. 2006), especially when NO_2 and particles ($PM_{2.5}$) are used as proxies for traffic-related air pollution. Although this is in accordance with the results of the present study, direct comparison is difficult as the mechanisms resulting in an episode of AF can differ from the mechanisms leading to development of incident AF (Waks and Josephson 2014).

A few studies have investigated associations between long-term exposure to air pollution and cardiac rhythm disturbances; a broad group of arrhythmia diagnoses and different cardiac structural and functional abnormalities, which besides AF also includes attacks of tachycardia, ventricular fibrillation, cardiac arrest and others. The studies on mortality from cardiac rhythm disturbances show inconsistent results (Beelen et al. 2009; Pope et al. 2004; Raaschou-Nielsen et al. 2012). However, it is difficult to make a direct comparison between the present as well as short-term studies and these studies, as most cardiac rhythm disturbances do not result in death; in the present study cohort, only 24 subjects with death due to AF during follow-up were registered. Only study, by Atkinson et al., investigated incident cardiac rhythm disturbances as a health outcome. In contrast to the present study, Atkinson et al. found no associations between long-term exposure to air pollution assessed as PM_{10}, NO_2, and O_3 by a dispersion model, and incidence of arrhythmias combined, although there was a significant positive association with SO_2 (Atkinson et al. 2013). One reason for the discrepant results could be the differences in outcome definitions. In the present study, we only investigated risk of AF, which was based on data from the Danish National Patient Registry corresponding to approximately 60 % of all the diagnoses included in arrhythmia outcome in the study by Atkinson et al. This could have diluted a potential association between air pollution and AF. Another reason for discrepant results could be the different approach to estimation of exposure to air pollution. In the study by Atkinson et al., the resolution was in 1 x 1 km grids and only one postcode for each cohort member. In the present study we applied a dispersion model with much higher resolution to estimate exposure at the front door of each included address, taking into account street configurations and traffic data for the road links adjacent residence, and, thus, potentially a more precise estimation of residential exposure to air pollution. In addition, the present study included exposure at both present and historical addresses for all cohort members. The recruitment of the cohort for study and outcome ascertainment was also different in the two studies. We used a population-based approach with invitation of a random sample and used the highly complete Danish National Patient Register, whereas Atkinson et al. recruited their cohort from 205 clinical practises in England.

We found that associations between NO_2 and AF were not modified by sex, smoking status, hypertension or myocardial infarction and no differences in estimates according to age at AF diagnosis. However, there were some indications of a stronger association among participants with hypertension at baseline, suggesting that hypertensive people are more susceptible to air pollution exposure in relation to developing AF. Hypertension is one of the strongest risk factors of AF and long-term hypertension is associated with abnormal atrial volume, structure and function (Schnabel et al. 2009). These abnormalities may contribute to increased susceptibility of subjects with hypertension to air pollution. Interestingly, despite air pollution being a known risk factor of myocardial infarction (Wolf et al. 2015), which is an established risk factor of AF (Schnabel et al. 2015), the presence of a myocardial infarction before a diagnosis of AF did not modify the association between air pollution and AF.. However, only about 10 % of the cases had a diagnosis of myocardial infarction, and the event rate may therefore not be sufficient to detect a potential effect modification.

The associations observed between exposure to air pollution and risk of AF are relatively small compared to already established risk factors such as obesity and alcohol consumption

(Supplemental Table S2) (Samokhvalov et al. 2010; Wanahita et al. 2008). However, even the relatively small association with AF observed may have substantial impact on the population given the widespread nature of air pollution.

The strengths of the present study include the prospective design with information on various potential lifestyle and socioeconomic confounders, the large number of cases, inclusion of only the first hospitalization of AF and access to residential address history. Furthermore, cases with AF were identified using a high quality nationwide hospital register, which has been found to have a very high positive predictive value with regard to the AF diagnosis (93 %) (Rix et al. 2012).

The present study also has some limitations. Estimation of air pollution was based on a model, and although the AirGIS dispersion model is a standard, validated method, estimation of exposure is inevitably associated with some degree of uncertainty. As the exposure model does not distinguish between cases and non-case cohort members, such misclassification is likely to be non-differential. Also, we lacked information on factors that influence the personal exposure to air pollution, including time spend at home, information on commuting and occupational exposure, which may result in exposure misclassification. Furthermore, we may have missed some AF cases as we were able only to include symptomatic AF, which led to hospital admission and/or outpatient visits. Therefore, the true incidence of AF is most likely higher than the observed incidence. However, in Denmark most patients with clinical symptoms of AF are referred to a hospital for further evaluation. Also, the date of diagnosis registered in the hospital register used might be somewhat different than the actual date of onset, which might underestimate the true effect (Lokken et al. 2009). Finally, we cannot rule that residual confounding may be present. Although we adjusted for many risk factors for AF, adjustment resulted in only minor changes in the estimates, suggesting that residual confounding is not a major concern in the present study, though residual confounding by unmeasured characteristics is always a risk.

The present study is based on an urban cohort of elderly people and results may, therefore, not be readily generalizable to the general population.

Conclusion

In conclusion, the study found a linear association between long-term exposure to traffic-related air pollution and risk of incident AF.

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Disclosures

None.

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Table 1. Baseline characteristics for the Diet, Cancer, and Health cohort according to low ($NO_2 < 15$ $\mu g/m^3$), medium ($15 \leq NO_2 < 20$ $\mu g/m^3$) and high ($NO_2 \geq 20$ $\mu g/m^3$) exposure to NO_2 at enrolment of 50,399 cohort participants.

Characteristic at enrolment	Total cohort (n = 50,399)	$NO_2 < 15$ $\mu g/m^3$ (n =15,652)	$15 \leq NO_2 < 20$ $\mu g/m^3$ (n = 18,432)	$NO_2 \geq 20$ $\mu g/m^3$ (n = 16,315)
Men (%)	47.0	48.9	46.6	45.5
Age (years)	56.2 (50.8-64.2)	55.8 (50.7-64.0)	56.5 (50.8-64.3)	56.3 (50.7-64.2)
Length of school attendance (%)				
≤ 7 years	33.1	34.0	33.2	32.3
8-10 years	46.4	45.4	46.8	47.0
≥ 10 years	20.5	20.6	20.1	20.8
Socioeconomic position (%)[1]				
Low	21.0	27.8	17.6	18.5
Medium	64.7	64.7	65.9	63.5
High	14.2	7.6	16.5	18.0
Smoking status (%)				
Never	36.1	37.9	36.9	33.5

Former	36.4	28.7	28.2	25.6
Current	27.5	33.4	34.9	40.9
Among present and former smokers				
Smoking duration (years)	33.0 (7.0–46.0)	35.0 (7.0–46.0)	32.0 (7.0–46.0)	33.0 (3.0-46.0)
Smoking intensity (g/day)[2]	14.7 (3.8-34.3)	14.5 (3.7-35.3)	14.6 (3.7-33.8)	15.0 (4.0-33.9)
Alcohol consumption (%)	97.8	98.2	97.7	97.4
Alcohol intake (g/day)	13.2 (1.1-64.4)	12.8 (1.2-59.7)	13.2 (1.1-64.6)	13.7 (1.0-69.2)
Physical active (%)	54.2	56.6	54.8	51.2
Sport during leisure time (h/week)[3]	2.0 (0.5-7.0)	2.0 (0.5-7.0)	2.0 (0.5-6.5)	2.0 (0.5-7.0)
BMI (kg/m^2)	25.5 (20.4-33.3)	25.5 (20.5-33.0)	25.6 (20.5-33.5)	25.6 (20.3-33.5)
Waist circumference (cm)	88.0 (69.0-110.0)	89.0 (69.5-109.5)	89.0 (69.0-110.0)	88.0 (69.0-110.0)
Hypertension (%)	49.9	48.2	50.6	50.7
History of myocardial infarction (%)	5.9	5.7	5.9	6.0

Values are medians (5th – 95th percentiles) unless otherwise stated
[1]Area level socioeconomic position based on municipality information on education, work market affiliation and income.
[2]The average amount of tobacco smoked per day during lifetime [3]Among active

Table 2 Association between mean 10-years residential exposure to NO_2 and NO_x and risk of atrial fibrillation.

Air pollution	Cases	Crude IRR (95% CI) [1]	Adjusted IRR (95% CI) [2]
10-year mean NO_2			
Q1: < 11.4 $\mu g/m^3$	540	1.00 (ref.)	1.00 (ref.)
Q2: 11.4-13.3 $\mu g/m^3$	539	1.05 (0.93-1.19)	1.06 (0.94-1.20)
Q3: 13.3-16.1 $\mu g/m^3$	541	1.10 (0.97-1.24)	1.10 (0.97-1.25)
Q4: 16.1-20.1 $\mu g/m^3$	540	1.24 (1.10-1.39)	1.24 (1.09-1.40)
Q5: ≥ 20.1 $\mu g/m^3$	540	1.19 (1.05-1.34)	1.19 (1.04-1.36)
Linear trend per 10 $\mu g/m^3$ [3]	*2,700*	*1.08 (1.02-1.15)*	*1.08 (1.01-1.14)*
10-year mean NO_x			
Q1: < 13.8 $\mu g/m^3$	539	1.00 (ref.)	1.00 (ref.)
Q2: 13.8 < 16.9 $\mu g/m^3$	540	0.99 (0.87-1.11)	0.99 (0.87-1.12)
Q3: 16.9 < 20.8 $\mu g/m^3$	540	1.20 (1.06-1.35)	1.20 (1.06-1.36)
Q4: 20.8 < 29.6 $\mu g/m^3$	541	1.20 (1.06-1.35)	1.19 (1.05-1.35)
Q5: ≥ 29.6 $\mu g/m^3$	540	1.17 (1.03-1.32)	1.16 (1.02-1.32)

IRR, Incidence rate ratio; CI, confidence interval; Q1-Q5, quintiles 1-5.
[1] Adjusted for age
[2] Adjusted for age, sex, body mass index, waist circumference, smoking status, smoking duration, smoking intensity, intake of alcohol, sport during leisure time, length of school attendance, area level socioeconomic position and calendar year.
[3] Linear association per 10 $\mu g/m^3$ increase in NO_2 exposure

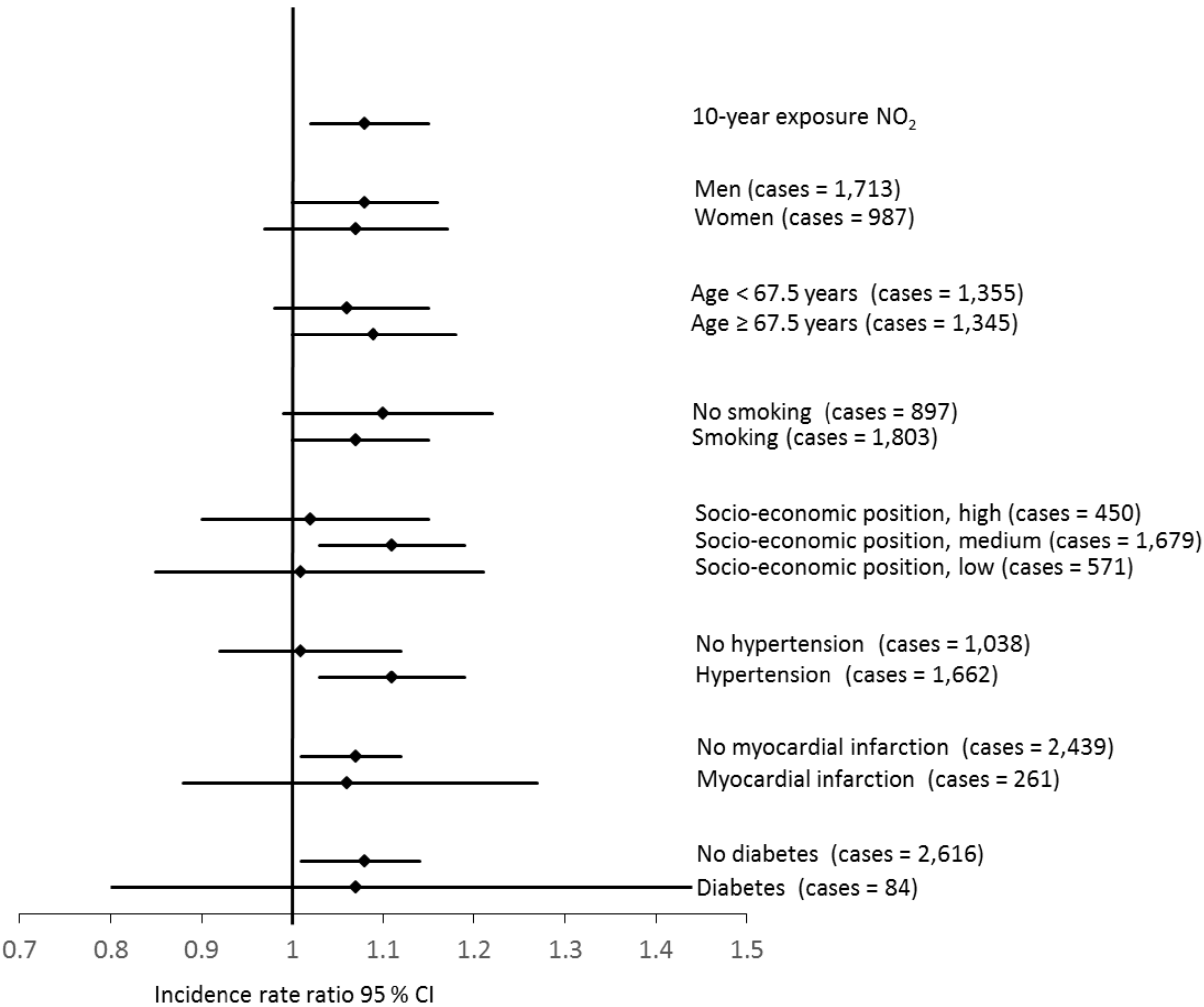

Figure 1 Associations (incidence rate ratios) between 10-years' time-weighted exposure to NO_2 ($\mu g/m^3$) and risk for atrial fibrillation in different subgroups. Analyses were adjusted for age, sex, lifestyle factors (BMI, waist circumference, smoking status, smoking duration, smoking intensity, intake of alcohol, physical activity), socioeconomic position (length of school attendance, area level socioeconomic position) and calendar year.